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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/895,713	06/29/2001	David H. Sachs	59056-131CON	7385

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EXAMINER
WEHBE, ANNE MARIE SABRINA

ART UNIT	PAPER NUMBER
1632	13

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/895,713	Applicant(s) Sachs
	Examiner Anne Marie Wehbé	Art Unit 1632

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Apr 9, 2003*.

2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *22, 23, 25-28, 30-35, and 37-58* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *22, 23, 25-28, 30-35, 37-39, 41-52, and 54-58* is/are rejected.

7) ☒ Claim(s) *40 and 53* is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Applicant's amendment received 4/9/03 has been entered. Claims 24, 29, and 36 have been canceled ,and new claims 40-58 have been entered. Claims 22-23, 25-28, 30-35, and 37-58 are pending in the instant application. An action on the merits follows.

Those sections of Title 35, US code, not included in the instant action can be found in previous office actions.

Claim Rejections - 35 USC § 112

The rejection of claims 22-39 under 35 U.S.C. 112, first paragraph, for lack of enablement is maintained in modified form over claims 23, 30, 34-35, 37-39, 41, 43, 48, 52, and 54-58, and withdrawn over claims 22, 25-28, and 31-33. Applicant's amendment and arguments have been fully considered but have not been found persuasive in overcoming the following grounds of rejection of the claims for reasons of record as discussed in detail below.

In view of applicant's arguments, the following subject matter has been determined to be enabled by the specification. Methods for inhibiting a mammalian recipient's ability to mount an immune response against an MHC class I antigen expressed on donor tissue derived from a mammal of the same species as the recipient, comprising providing the recipient with recipient

bone marrow hematopoietic stem cells having inserted therein DNA encoding an MHC class I antigen, wherein the MHC class I antigen is the same antigen expressed by donor tissue, wherein the expression of said MHC class I antigen in the recipient inhibits the recipient's ability to mount an immune response against said MHC class I antigen when expressed by donor tissue.

In addition, it is noted that the rejection of claims 22, 25-28 and 31-33 has been withdrawn in view of applicant's argument that the stem cells can be used to inhibit immune responses against the particular MHC class I antigen expressed by the stem cells. Claims 23, 30, 43, and 48 remain rejected based on the intended use language which states that the cells are capable of inhibiting a recipient's immune response to a tissue from a donor.

The applicant argues that the claimed cells and methods are limited to the inhibition of a recipient's ability to mount an immune response against a particular donor MHC class I antigen and are not directed to the inhibition of all recipient responses. Based on applicant's interpretation of the claims, the applicant states that the working examples using congenic mouse strains clearly demonstrates that in the absence of "confounding responses", i.e. responses against other antigens expressed by allogeneic tissue such as additional MHC class I antigens and MHC class II antigens, the expression of a single donor MHC class I molecule by recipient bone marrow cells can inhibit immune responses against that single MHC class I antigen. The applicant further states that they do not argue that there would not be responses to other antigens if additional loci were mismatched. The applicant also states that sibling donor-recipient combinations may differ at only a single class I allele. The office finds these arguments compelling in regards to applicant's

method claims 40 and 53 which clearly state that the donor MHC class I gene expressed by the recipient cells is the same as that expressed by a donor tissue, and that the intended result of the method is the inhibition of immune responses against the particular donor MHC class I gene expressed by the transfected recipient cells. Based on applicant's statements, these claims do not read on the inhibition of immune responses against other MHC class I or II molecules expressed by the donor tissue, or on the prevention of graft rejection of donor tissue.

Claims 23, 30, 43, and 48, however, are not so limited. The claims recite the inhibition of the recipient's immune response to donor tissue. As such the encompass the inhibition of any and all immune responses against any mismatched MHC class I or II antigen present on the donor tissue. The previous office action provided substantial discussion regarding the lack of enablement for inhibiting immune responses against mismatched MHC class I or II antigen present on the donor tissue which are not expressed by the recipient bone marrow cells. The applicant has not traversed these arguments and in fact appears to agree with the office since they state that they do not argue that there would not be responses to other antigens if additional loci were mismatched, see applicant's response, page 9. Therefore, the rejection of record is maintained over claims 23, 30, 43, and 48. However, this grounds of rejection can be overcome by amending the claims to either delete the intended use language or to indicate that the cells are capable of inhibiting the immune response against the donor MHC class I molecule expressed by the recipient cells, rather than any immune response against a donor tissue.

Regarding claims 34-35, 37-39, 41, 52, and 54-58, the applicant has amended these claims to recite wherein the MHC class I antigen expressed by the recipient cells is the same as "or closely related to" that expressed by donor tissue. This is a new limitation. The specification does not provide a definition or description of the structural features of MHC class I antigens which qualify as "closely related" to other MHC class I antigens. As discussed in the rejection of these claims under 35 U.S.C. 112, second paragraph below, it is unclear whether this limitation reads on any MHC class I antigen which has a similar structure, i.e. any MHC class I antigen from any species, or which is from the same species, or which is simply located nearby in the species genome. The previous office action provided a detailed discussion concerning the lack of enablement in the specification for inducing cross-tolerance to donor MHC antigens which are not expressed by the recipient hematopoietic cells. The applicant has not provided any arguments traversing these grounds of rejection. Therefore, the rejection of record is maintained over amended claims 34-35, 37-39, 41, 52, and 54-58. This grounds of rejection can be overcome by deletion of the phrase, "or closely related to".

The rejection of claim 29 under 35 U.S.C. 112, second paragraph, for indefiniteness with withdrawn in view of applicant's cancellation of the claim.

Applicant's amendment to claim 34 and addition of new claims has resulted in the following new grounds of rejection.

Claims 34-35, 37-39,41,52, and 54-58 are newly rejected under 35 U.S.C. 112, second paragraph as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The applicant claims, amended or new, recite, "said MHC class I antigen being the same as or closely related to that expressed by donor tissue". The metes and bounds of the phrase "closely related" in regards to the MHC class I antigen cannot be determined. The specification does not define what constitutes an MHC class I antigen which is closely related to another MHC class I antigen. It is unclear whether this phrase encompasses MHC class I antigens which are related by structure, or by species, or by some other criteria. As such, this language renders the claims indefinite.

Claim Rejections - 35 USC § 103

The rejection of claims 22, 23, and 28 are rejected under 35 U.S.C. 103(a) as being unpatentable over Madsen et al. (1989) Transpl. Proc., Vol. 21 (1), 477 in view of Pullen et al. (1986) J. Immunol., Vol. 137, 1359-1365 is maintained. Applicant's amendment and arguments have been fully considered but have not been found persuasive in overcoming the rejection of the claims for reasons of record as discussed in detail below.

The applicant argues that Madsen teaches the transfection of L cells and does not teach or suggest the transfection of hematopoietic cells. The applicant further argues that Pullen et al. also does not teach the transfection of hematopoietic cells, or provide motivation for transfecting

hematopoietic cells with an MHC class I gene. In response, the office has relied on the teachings of Madsen et al. for transfecting cells with either class I or class II genes from a H-2^b mouse (Madsen et al., page 477, column 1, paragraph 2). In addition, Madsen et al. was cited for providing motivation for transfecting cells with either class I or class II genes of a different haplotype by teaching that the presence of either a non-identical MHC class I or class II gene on cells or tissues prolongs the survival of organ grafts of the same haplotype as the transfected MHC gene in animals (Madsen et al., page 477, column 2, paragraph 2). The office acknowledged in the previous office action that Madsen et al. does not specifically teach transfecting hematopoietic cells. For this reason, the office supplemented the teachings of Madsen et al. with the teachings of Pullen et al.

Contrary to the suggestion by the applicant that Pullen et al. does not teach the transfection of hematopoietic cells, Pullen et al. clearly teaches the transfection of C57BL6 bone marrow cells with an MHC gene (Pullen et al., page 1359, abstract, and pages 1359-1360, bridging paragraph). Bone marrow cells were well known at the time of filing to contain hematopoietic stem cells. Further, the applicants themselves disclose the transfection of bone marrow cells in the specification. The fact that bone marrow cells can differentiate into more mature cell types in culture does not take away from the clear teachings in Pullen et al. to transfect the bone marrow cells **prior** to their differentiation to other cell types such as macrophages. In addition, how Pullen et al. decided to use the transfected hematopoietic cells is irrelevant to the instant claims, because the instant claims are simply product claims. As stated in the previous

office action, " in apparatus, article, and composition claims, intended use must result in a structural difference between the claimed invention and the prior art in order to patentably distinguish the claimed invention from the prior art." *In re Casey*, 152 USPQ 235 (CCPA 1967); *In re Otto* , 136 USPQ 458, 459 (CCPA 1963)(MPEP 2111.02). Furthermore, applicant's argument that Pullen does not teach MHC class I genes is not persuasive because Madsen et al., the primary reference, teaches the transfection of either MHC class I or MHC class II genes into cells.

In response to applicant's argument that there is no motivation or suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 19880; *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). Madsen et al. was cited in the previous office action for providing motivation for transfecting cells with either class I or class II genes of a different haplotype by teaching that the presence of either a non-identical MHC class I or class II gene on cells or tissues prolongs the survival of organ grafts of the same haplotype as the transfected MHC gene in animals and Pullen et al. was cited for providing motivation for transfecting bone marrow stem cells over other types of cells by teaching that bone marrow is an excellent population of cells for genetic manipulation because these cells can be extracted from an animal, grown in culture, and then successfully reimplanted

into the animal. Thus, based on the motivation to use bone marrow stem cells for genetic manipulation provided by Pullen et al., and the motivation to transfect cells with MHC class I or II genes of a different haplotype provided by Madsen et al., it would have been *prima facie* obvious to the skilled artisan at the time of filing to transfect bone marrow hematopoietic stem cells with genes for MHC class I of a different haplotype using the well-known techniques taught by Madsen and Pullen. Furthermore, based on the successful expression of MHC in transfected bone marrow observed by Pullen et al., the skilled artisan would have had a reasonable expectation of success in transfecting bone marrow stem cells with a vector encoding an MHC class I molecule of a different haplotype.

Finally, the applicant is reminded that it is well established in case law that a reference must be considered not only for what it expressly teaches, but also for what it fairly suggests. *In re Burkel,* 201 USPQ 67 (CCPA 1979). Furthermore, in the determination of obviousness, the state of the art as well as the level of skill of those in the art are important factors to be considered. The teaching of the cited references must be viewed in light of these factors. It is also noted, that the test for combining references is not what the individual references themselves suggest, but rather what the combination of disclosures taken as a whole would have suggested to one of ordinary skill in the art. *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971). For the purpose of combining references, those references need not explicitly suggest combining teachings, much less specific references. *In re Nilssen*, 7 USPQ2d 1500 (Fed. Cir. 1988). Therefore, for reasons of record as discussed in detail above, the rejection is maintained.

The rejection of claims 24-27 and 29-33 under 35 U.S.C. 103(a) as being unpatentable over Madsen et al. (1989) Transpl. Proc., Vol. 21 (1), 477 in view of Pullen et al. (1986) J. Immunol., Vol. 137, 1359-1365, as applied to claims 22, 23, and 28 above, and further in view of Bernstein et al. (1986) Cold Spring Harbor Symp. on Quant. Biol., Vol. LI, 1083-1091 is maintained over pending original, amended, or new claims 25-27, 30-33, and 42-51.

The applicant argues that the primary references, Madsen and Pullen, fail to suggest the claimed invention and that Bernstein does not supply the missing teachings. Applicant's arguments regarding Madsen and Pullen et al. have been addressed in detail above and have not been found persuasive. In regards to Bernstein et al., Bernstein et al. was cited for teaching that retroviral vectors, particularly Moloney-based retroviral vectors, can be used to introduce DNA into murine or human hematopoietic stem cells in culture (Bernstein et al., page 1084, Figure 1, page 1084-1085, bridging paragraph, and page 1085, column 1). In addition, Bernstein et al. provides motivation for using retroviral vectors rather than other vectors known at the time of filing by teaching that the low frequency of stem cells in the hematopoietic system necessitates the use of highly efficient gene transfer techniques, and that retroviruses are ideally suited as gene transfer vectors due to their high infection efficiency, stable integration into the host genome, and high level of gene expression. The suggestion to transfect cells with MHC class I molecules is provided by Madsen et al., see above. Therefore, the rejection of record is maintained.

Claims 40 and 53 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims. Applicant's amendment and arguments have been fully considered but have not been found persuasive in overcoming the rejection of the claims for reasons of record as discussed in detail below.

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication from the examiner should be directed to Anne Marie S. Wehbé, Ph.D., whose telephone number is (703) 306-9156. The examiner can be reached Mon-Fri from 10:30-7:00 EST. If the examiner is not available, the examiner's supervisor, Deborah Reynolds, can be reached at (703) 305-4051. General inquiries should be directed to the group receptionist whose phone number is (703) 308-0196. The technology center fax number is (703) 308-4242, the examiner's direct fax number is (703) 746-7024.

Dr. A.M.S. Wehbé

ANNE M. WEHBE' PH.D
PRIMARY EXAMINER